PATHOGENESIS AND THERAPY OF THE MUSCULAR DYSTROPHIES

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P.T.

National Institute of Neurological Disorders and Stroke
National Institute of Arthritis and Musculoskeletal and Skin Diseases

PURPOSE

The National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) encourage investigator-initiated research grant applications to study the pathogenesis and therapy of the various forms of muscular dystrophy in children and adults. Responses to this program announcement may include studies in appropriate animal models or preclinical or clinical studies in patients with facioscapulohumeral dystrophy (FSH), limb-girdle muscular dystrophy (LGMD), myotonic dystrophy, congenital muscular dystrophy (CMD), Emery-Dreifuss muscular dystrophy (EMD), Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), or other forms of muscular dystrophy.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention goals of "Healthy People 2000," a PHS-led national activity for setting priorities. This program announcement, Pathogenesis and Therapy of the Muscular Dystrophies, is related to the priority area chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local

governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

The support mechanisms for grants in this area will be the investigator-initiated research project grant (R01) and the program project grant (P01). The Principal Investigator or program director, as well as any participating investigators, will plan, direct, and perform the research. Applicants for program projects are requested to contact the NINDS or NIAMS representative listed under INQUIRIES as early as possible in the planning stages. Applicants must receive permission from the NINDS or NIAMS prior to the submission of an application requesting more than $500,000 in direct costs per year for any year of the proposed study.

RESEARCH OBJECTIVES

Background

The muscular dystrophies are a heterogeneous group of inherited neuromuscular diseases characterized by weakness and wasting of muscles. Precise incidence and prevalence figures are difficult to determine, and most individual forms of muscular dystrophy are rare. The total impact, however, is high, as tens of thousands of people are affected with some type of muscular dystrophy in the United States alone. Although genes responsible for many forms of muscular dystrophy have been identified, much more research is needed to discover the pathogenic mechanisms involved and develop effective treatments.

Facioscapulohumeral (FSH) muscular dystrophy is an autosomal dominant form that initially affects muscles of the face (facio), scapula (scapulo) and upper arms (humeral). Symptoms may develop in early childhood and are usually noticeable in the teenage years. A progressive skeletal muscle weakness usually develops in other areas of the body as well; often the weakness is asymmetrical. Life expectancy is normal, but some affected individuals become severely disabled. Nearly all cases are associated with a distal 4q35 deletion. Because there are no known genes in this region, a novel position effect has been postulated to explain the disease phenotype.

The limb-girdle muscular dystrophies (LGMD) are genetically heterogeneous, with both dominant and recessive forms reported. All limb-girdle muscular dystrophies show a similar distribution of muscle weakness, affecting both upper arms and legs. The recessive LGMDs are more frequent

than the dominant forms, and usually have childhood or teen-age onset. The dominant LGMDs usually show adult onset. In addition to muscle weakness, the creatine kinase (CK) values are elevated in affected individuals usually 4-10 times the normal laboratory values. Four of the recessive forms have been associated with defects in genes coding for the sarcoglycan complex, which along with dystrophin helps anchor muscles to the extracellular matrix. More devastating mutations in these same genes can cause severe childhood autosomal muscular dystrophy (SCARMD).

Myotonic dystrophy is the most common form of muscular dystrophy in adults. It is dominantly inherited and affects brain, lens, and heart in addition to skeletal muscles. Myotonic dystrophy is one of the growing number of triplet repeat disorders; it is associated with a CGT expansion in an untranslated region of 19q13.3. Larger numbers of repeats are found in more severely affected individuals, and the number of repeats tends to increase from generation to generation, thus explaining earlier age of onset and increased symptoms in subsequent generations (anticipation). The product of the myotonic dystrophy locus on chromosome 19 is a novel form of protein kinase. The function of this specific kinase is unknown, and it has yet to be determined whether a defect in this protein leads to the myotonic dystrophy phenotype.

Emery-Dreifuss muscular dystrophy (EMD) is a sex-linked form characterized by wasting of shoulder, upper arm, and shin muscles. Joint deformities are common. It also inflicts serious cardiac problems that can result in premature and sudden death. Cardiac involvement may also cause premature death in female carriers. The responsible sex-linked gene has been located (Xq28), and it has been found to code for a previously unknown protein, called emerin, associated with the muscle membrane Emerin is normally found in both and skeletal muscle and heart muscle. Different mutations of this gene may result in the absence of emerin and thus the disease. A few cases have been found in which emerin is normal, suggesting genetic heterogeneity.

Congenital muscular dystrophy (CMD) is a heterogeneous group of severe autosomal-recessive neuromuscular diseases with early clinical onset. Manifestations of CMD are evident at birth or in the first few months of life and consist of muscle weakness and hypotonia, delayed motor milestones, severe and early contractures, and, often, joint deformities. Some cases of CMD have been attributed to absence of merosin, a component of laminin. Laminin is the extracellular component of the complex that, together with dystrophin and associated glycoproteins, anchors the muscle cell. The same gene is responsible for one of the animal models of muscular dystrophy, the dy/dy mouse.

Duchenne muscular dystrophy (DMD) is the most common form, affecting approximately one in 3,500 male births. The sex-linked disease is characterized by muscle necrosis and regeneration. Eventually, the regeneration cannot keep up with the necrosis, resulting in progressive muscle fiber loss. Affected boys are usually wheelchair-bound by age 12, with death often occurring by age 20 from cardiac or respiratory problems. The genetic defect leads to missing or abnormal dystrophin, an important structural protein unknown until the gene was discovered. Recent animal model studies have suggested that utrophin, a structurally similar protein present at the neuromuscular junction, may somehow be made to compensate for dystrophin.

A milder variant, Becker muscular dystrophy (BMD), is caused by a different defect in the DMD gene, usually an internal in-frame deletion that produces truncated but partially functional dystrophin. Symptoms are similar to DMD, with muscles of the pelvis, upper arms, and upper legs affected first, but they are more variable than in DMD Some affected people are able to walk only until early adulthood, others to an advanced age. Survival in some is to middle age but others have survived more than 80 years. Heart trouble may develop in early adulthood.

Scope and Objectives

Investigators with diverse scientific interests are invited to apply their expertise to basic and applied research to enhance our understanding of the pathogenesis of the muscular dystrophies, including the development of appropriate animal models. Examples that illustrate possible areas of research to be considered are presented below. They are intended only to provide a broad direction for research into several of the muscular dystrophies and should be considered illustrative and not restrictive. The following general examples are relevant to several forms of muscular dystrophy:

- examine genetic heterogeneity, and search for additional candidate genes

- examine genotype/phenotype correlations within and between families

- further pursue the development of appropriate animal models

- develop improved diagnostic procedures

- study pathogenic mechanisms leading from gene defects to muscular dystrophy phenotypes

- study the involvement of apoptotic cell death in the process of muscle fiber degeneration

o attempt to improve protein expression from transplanted myoblasts to a useful level

o continue to explore the development of new types of therapy, including gene therapy

Some possible areas of research that are specific to one form of muscular dystrophy include:

o facioscapulohumeral muscular dystrophy. continue the sequencing of the entire 4q35 region; investigate the position effect hypothesis and its basis in chromatin structure.

o limb-girdle and severe childhood autosomal recessive muscular dystrophy: examine pathogenic mechanisms in cases not caused by sarcoglycan defects; study the role of dystrobrevin deficiency in the pathogenesis

o myotonic dystrophy: study the pathogenic mechanisms involved in the CGT triplet repeat; identify factors other than length of triplet repeat that are related to phenotypic expression

o Emery-Dreifuss muscular dystrophy: determine the function of emerin in skeletal and cardiac muscle; determine the extent to which other genes can cause EMD-like symptoms

o congenital muscular dystrophy: investigate the role of merosin with other proteins in peripheral myelinogenesis; determine how different molecular defects in merosin lead to variable phenotypes

o Duchenne and Becker muscular dystrophy: study the development and function of the dystrophin-glycoprotein complex; investigate the compensatory effects observed with the overexpression of utrophin

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513), and in the NIH GUIDE FOR GRANTS AND CONTRACTS, Volume 23, Number 11, March 18, 1994.

Investigators may also obtain copies from these sources or from the program staff or contact person listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev.5/95) and will be accepted at the standard application deadlines as indicated in the application kit. These forms are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: asknih@od.nih.gov.

Check "YES" in item 2a on the face sheet of the application and type "Pathogenesis and Therapy of the Muscular Dystrophies."

Applicants for the P01 should contact the NINDS and NIAMS program officers listed under INQUIRIES to discuss their planned projects and to request the Institute's guidelines for program project applications.

Submit a signed, typewritten original of the application, including the Checklist, plus five signed photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

If the application is for a program project, submit the original and three copies to the Center for Scientific Review. An additional two copies must be sent to Dr. Nichols or Dr. Lymn at the

addresses listed under INQUIRIES to expedite processing and review of applications for multidisciplinary efforts.

REVIEW CONSIDERATIONS

Applications that are complete will be evaluated for scientific and technical merit by an appropriate peer review group convened in accordance with NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit will be discussed, assigned a priority score, and receive a second level review by the National Advisory Council of the assigned Institute(s).

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written review, comments on the following aspects of the application will be made in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in the assignment of the overall score.

o Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

o Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

o Innovation: Does the project employ novel concepts, approaches or methods?
Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

o Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

o Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

o Appropriateness of the proposed budget and duration in relation to the proposed research.

o Adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will be evaluated.

o The initial review group will also examine the provisions for the protection of human and animal subjects, and the safety of the research environment.

o Availability of special opportunities for furthering research programs through the use of unusual talent resources, populations, or environmental conditions in other countries which are not readily available in the United States or which provide augmentation of existing United States resources.

o For program project and research center grant applications, additional factors to be considered during the review would include the efficacy of the collaboration, the commitment of the participants to the collaboration, the design and responsibilities of the coordinating center and the cost effectiveness of the collaborative effort.

AWARD CRITERIA

Applications will compete for available funds with all other approved applications. The following will be used in making funding decisions:

o Scientific and technical merit of the proposed project as determined by peer review

o Availability of funds

o Program balance among research areas of the announcement

INQUIRIES

Written, telephone, and e-mail inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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Direct inquiries regarding fiscal matter to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos.93.853 , 93.854, and 93.846. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-150, 42 USC 241 and 285) and administered under PHS grant policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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